REMARKS/ARGUMENTS

Discussion of Claim Amendments

Claims 1, 12, 14, 27, 29, 31, 33, and 35-36 have been amended to further sharpen the claim language. New claims 76-78 have been added and are directed to embodiments of the invention. The new claims belong to the elected Group III, and are generic to the elected species. Claims 3-5, 8-10, 15, 16, 21, 22, 24, 26, 28, 30, 32, 34, and 38-74 have been cancelled without prejudice to the possible filing of a divisional application directed to the subject matter of the canceled claims. No new matter has been added by way of these amendments.

The Office Action

The Office Action sets forth the following grounds for rejection:

(1) claims 1, 2, 6, 7, 11-14, 17-20, 23, 25, 27, 29, 31, 33, 35-37, and 75 are rejected under 35 U.S.C. § 112, first paragraph, for an alleged failure to satisfy the enablement requirement;

(2) claims 1, 2, 6, 7, 11-14, 17-20, 23, 25, 27, 29, 31, 33, 35-37, and 75 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite; and

(3) claims 1, 2, 6, 7, 11-14, 17-20, 23, 25, 27, 29, 35-37, and 75 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over U.S. Patent No. 6,593,353 (Gudkov et al.).

Discussion of Rejections

(1) Enablement Rejection

Claims 1, 2, 6, 7, 11-14, 17-20, 23, 25, 27, 29, 31, 33, 35-37, and 75 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. According to the Office, the specification does not enable a person of skill in the art to make and use the invention commensurate in scope with the rejected claims. Specifically the Office contends that the specification does not provide enablement for all cell protection factors which are capable of being linked to a bone targeting agent, for all bone targeting agents, and for all cleavable linkers. Applicants respectfully traverse the rejection for the reasons stated herein.

Applicants submit that claims 1, 2, 6, 7, 11-14, 17-20, 23, 25, 27, 29, 31, 33, 35-37, and 75, which are directed to a method of inhibiting cell death in a mammal, are indeed enabled by the specification. For example, paragraphs [0056] and [0057] of the specification describe a variety of cell protection factors of the present invention, including factors that inhibit the activity of tumor suppressor genes, such as RB1, p53, INK4a, APC, BRCA1, and BRCA2 to name a few, while paragraphs [0083] thru [0090] of the specification describe numerous bone targeting agents, such as ligands that bind hydroxyapatite. In addition, paragraphs [0091] thru [0093] provide ample discussion regarding cleavable linkers, including nucleophilic and electrophilic reacting groups.

According to the MPEP (e.g., see 2164.03), the "amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art" and that the "more that is known in the prior art about the nature of the invention,...the less information needs to be explicitly stated in the specification." Thus, based on the information provided in the specification, applicants respectfully submit that the amount of guidance or direction provided fully meets the statutory requirement of enablement.

Further, the art, with respect to the use of cell protection factors for inhibiting cell death, for example is highly predictable. A google search for "cell protection factors" or "cell death inhibitors," for example, provides an enormous number of inhibitors, including p35, Bcl inhibitors, and pifithrin. There is no uncertainty with respect to their efficacy. Applicants' invention delivers such inhibitors to the targeted site. If any, the degree of predictability of use is enhanced by the *targeted delivery* invented by the present applicants. Thus, based on the above facts, applicants respectfully submit that the specification is enabling for the cell protection factors as presently claimed.

In view of the foregoing, Applicants respectfully submit that the skilled artisan, in view of the current disclosure and the state of the art, would be able to make and use the method of claim 1 without undue experimentation. The other rejected claims are dependent on claim 1. Based on the foregoing, Applicants respectfully request that the lack of enablement rejection of claims 1, 2, 6, 7, 11-14, 17-20, 23, 25, 27, 29, 31, 33, 35-37, and 75 be withdrawn. Furthermore, new claims 76-78 are patentable.

(2) Indefinite Rejection

Claims 1, 2, 6, 7, 11-14, 17-20, 23, 25, 27, 29, 31, 33, 35-37, and 75 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. According to the Office, it is unclear what conditions Applicants are referring to by the use of the phrase "a linkage that is cleaved under physiological conditions." Applicants respectfully traverse the rejections.

The definiteness of a claim must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one of ordinary skill in the art at the time the invention was made. See, e.g., *In re Marosi*, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983); *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 221 USPQ 1 (Fed. Cir. 1984); *W. L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983); *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 53 USPQ 2d 1225 (Fed. Cir. 1999); and *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

Based on the specification it is clear that "physiological conditions" as used in claim 1 should be construed to include all physiological conditions, including acidic, neutral, alkaline, or enzymatic conditions. For example, paragraph [0007] indicates that the cell protection factor is "cleaved under physiological conditions, whereby the cell protection factor is released from the bone targeting agent *in vivo* to inhibit cell death." Thus, physiological conditions clearly refer to conditions existing *in vivo*. Further, paragraph [0105] states that the linker is "cleavable under physiological conditions .... [such as] acidic physiological conditions." As a result, physiological conditions can refer to acidic conditions. In addition, it is clear that "physiological conditions" can also include those conditions existing in a mammal at a targeted location, such as at or near bone tissue. For example, paragraph [0091] states that:

> [u]pon administration to a mammal, the cell protection factor-bone targeting agent conjugate attaches to bone tissue (or another calcium-containing structure), the linkage between the moieties is cleaved, and the cell protection factor (e.g., temporary p53 inhibitor) is released in active form to inhibit cell death in the surrounding area.

Thus the specification teaches a specific environment at the bone and it is clear during bone resporption, an acidic environment would be presented due to the physiological process of bone resorption. For example, during bone resorption, the pH can be as low as 4.7.

Those of skill in the art would know the meaning of physiological conditions, based on both its use in the specification, the examples and the teachings of the art. Claim 1, therefore, defines the invention with a reasonable degree of precision, and meets the definiteness requirement. The other rejected claims are dependent on claim 1. In view of the foregoing, the indefiniteness rejection should be withdrawn. Claims 76-78 also should not be rejected on this basis.

(3) Obviousness Rejection

Claims 1, 2, 6, 7, 11-14, 17-20, 23, 25, 27, 29, 31, 33, 35-37, and 75 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Gudkov et al. Applicants respectfully traverse the rejection.

To establish a *prima facie* case for obviousness, the Office must satisfy three requirements. First, the prior art relied upon must contain some suggestion or incentive, coupled with knowledge generally available in the art at the time of the invention, that would have motivated those of ordinary skill in the art to modify a reference or combine the reverences. See *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006) (discussing rationale underlying the motivation-suggestion-teaching requirement as a guard against using hindsight in an obviousness analysis). Second, the proposed modification of the prior art must have had a reasonable expectation of success determined from the vantage point of the skilled artisan at the time the invention was made. In other words hindsight analysis is not allowed. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) ("While the idea of using a monkey gene to probe for a homologous human gene may have been obvious to try, many pitfalls existed that would have eliminated a reasonable expectation of successfully obtaining the EPO gene. Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious."). Third, the prior art reference or combination of references must teach or suggest all of the limitation of the claims. See *In re Wilson*, 424 F.2d 1382,

1385, 165 USPQ 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art.").

Applicants respectfully submit that the Office has not established a *prima facie* case for obviousness, since, among other things, the cited prior art reference does not teach or suggest all of the limitation of the claims. For example, claim 1 requires "a cell protection factor covalently linked to a bone targeting agent via a linkage that is cleavable under physiological conditions, whereby the cell protection factor is released from the bone targeting agent in vivo." Gudkov et al. does not teach or suggest a bone targeting agent. Further, Gudkov et al. does not teach or suggest a covalent link between a cell protection factor and a bone targeting agent. In addition, Gudkov et al. does not teach the release of a cell protection factor from a bone targeting agent.

The Office points to Gudkov et al.'s teaching of the use of a temporary p53 inhibitor in combination with "a carrier," in an erroneous attempt to show that there is a teaching or suggestion to generate a cell protection factor covalently linked to a bone targeting agent. However, "carrier," as referred to in Gudkov et al. is merely an excipient. For example, Gudkov et al., while discussing pharmaceutically formulations, states that "[t]he carriers are 'acceptable' in the sense of being compatible with *other ingredients* of the *formulation* and not deleterious to the recipient thereof." (Column 12, lines 2-5) (Emphasis added). These excipients are common items such as syrup, acacia, gelatin, lactose, sugar, talc, etc. to name only a few (see col. 12, lines 33 to col. 13, line 6). It is clear that a reference to such a pharmaceutical excipient would not motivate one of skill in the art to create a covalent bond between a temporary p53 inhibitor and another molecule, not to mention a bone targeting agent. Further, there is no suggestion or motivation to form a covalent link that is cleavable under physiological conditions to release the cell protection factor from the bone targeting agent, as required by claim 1.

The Office also points to Gudkov et al.'s teaching that the compounds therein "can form pharmaceutically acceptable salts with suitable cations" such as "phosphates" to erroneously argue that it would have been obvious to one of skill in the art to form a covalent bond between a cell protection factor and a bone targeting agent. (Column 11, lines 23-40). The fact that a reference notes that a compound "can form pharmaceutically acceptable salts"

would not motivate one of skill in the art to create a covalent bond between the compound and one of the provided exemplary counterions, especially since the formation of a covalent bond requires completely different chemistry from the formation of a salt between an acid and a base. Gudkov, et al. teaches (see col. 11, lines 23-40) that the compounds having acidic moieties can form pharmaceutically acceptable salts with suitable cat ions. Examples of such salts are hydrochloride, hydrobromide, sulfate, phosphate, hydrogen phosphate, etc. The bonds produced are *ionic,* not covalent. Further, the mere mention of a phosphate in the context of a "pharmaceutically acceptable salt" would not motivate one skilled in the art to choose a bone targeting agent as described in the present application.

There are huge gaps in the Office's contention of obviousness. The Office has failed to show motivation to bring in a bone targeting agent. The Office is employing extreme and impermissible hindsight. The Office is employing applicants' invention as a roadmap to find motivation. This is erroneous.

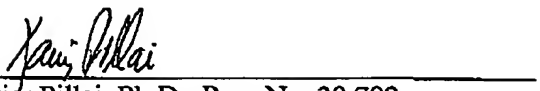
The Office has further failed to show motivation to bring in a covalent linkage to the unsuggested bone targeting agent. The Office has multiplied the error by a second hindsight reconstruction.

It is well established under the law that such extreme hindsight reconstruction is impermissible as it contravenes the statutory mandate of casting the inquiry of obviousness to the *time the invention was made* and not to the time of examination of the application.

Accordingly, the obviousness rejection of claim 1, and its dependent claims, should be withdrawn. Claims 76-78 also should not be rejected on this basis.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.



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